**REMARKS**

The Office Action dated April 13, 2006 has been carefully reviewed and the foregoing remarks are made in response thereto. In view of the above amendments and following remarks, Applicants respectfully request reconsideration and reexamination of this application and timely allowance of the pending claims.

By this Amendment, dependent claims 93-96, 105-110, 112-115, and 124-129 have been amended to replace the indefinite article "A" with the definite article "The." Claims 60, 80 and 99 have been amended to replace the phrase "gene sequences listed" with the phrase "genes and ESTs." Support for the amendments can be found, for example, at page 48, paragraph [0196] of the specification. Applicants respectfully submit that no new prohibited matter has been introduced by the amendments to the claims.

Upon entry of this amendment, claims 92-129 are pending in the application. In view of the amendments, Applicants respectfully request the rejections be withdrawn.

**Summary of Office Action**

1. Claims 92-129 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

2. Claims 92-129 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

3. Claims 92, 106 and 111 are rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Farr *et al.* (US Patent 5,811,231).

4. Claims 92, 97-101, 111 and 116-120 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Farr *et al.* (US Patent 5,811,231).

5. Claims 92, 97-101, 111, and 126 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Farr *et al.* (US Patent 5,811,231) in view of Lashkari *et al.* (PNAS, 94:13057-13062).

**Claim Rejections-35 U.S.C. § 112, First Paragraph (Lack of Enablement)**

The Examiner has rejected claims 92-129 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in a way to enable one skilled in the art to make or use the claimed invention.

The Examiner has rejected the claims based on the grounds that: "1) a database comprises data from liver, heart, kidney, testes, and brain and therefore one cannot predict hepatoxicity by comparing data from liver to the database; 2) the specification does not disclose whether the comparison in Tables 3A-3S is performed between expression profiles in liver or liver, kidney, testes, and brain; 3) not all genes of Table 1 are implicated in liver toxicity; 4) it is not disclosed whether comparison recited in claims 105 and 124 is performed with normal liver tissue or diseased tissue." (Pages 2-3 of the Office Action) Applicants respectfully traverse.

With respect to 1), Applicants respectfully submit that the specification provides ample guidance for one skilled in the art to practice the invention, *i.e.*, comparing gene expression data from liver tissue or cell samples to databases. The Examiner's attention is directed to page 32, lines 20-30, of the specification, where it discloses that the present invention includes relational databases containing sequence information for genes of Tables 1-3, as well as gene expression information from tissues or cells exposed to various standard toxins, such as those in Tables 3A-3S. At page 33, lines 18-26, the specification further discloses that the databases may be used to present information identifying the expression level in a tissue or cell of a set of genes comprising one or more of the genes in Tables 1-3. In Example 1 at page 36, the specification discloses that the hepatotoxins used in the assays were amitryptiline, ANIT, acetaminophen, carbon tetrachloride, cyproterone acetate, diclofenac, estradiol, indomethacin, valproate, or WY-1464. Quantitative gene expression levels obtained from the assays were presented in Tables 1-3 (see, for example, page 40, lines 4-28). Further, pages 3-15 set forth, in detail, the known liver toxicities induced by these same toxins. It is thus clear that the databases described as part of the present invention contain the gene sequence and expression information of Tables 1-3 which, in turn, contains the quantitative gene expression information from liver tissues or cells exposed to particular hepatotoxins such as amitryptiline, ANIT, acetaminophen, carbon tetrachloride, cyproterone acetate, diclofenac, estradiol, indomethacin, valproate, or WY-1464. Therefore, by comparing the gene expression profile from a liver tissue or cell sample exposed to a test compound to a database that contains gene expression information from liver cell or tissue samples as claimed, one skilled in the art would be able to predict the hepatoxicity of the test compound.

With respect to 2), Applicants respectfully submit, as pointed out in the previous

amendment, that all the genes disclosed in the Tables are pertinent to one or more toxic responses of the liver as claimed in the present invention. As clearly stated in the instant application, "the genes and gene expression information...provided in Tables 1-3, may be used to predict at least one toxic effect, including the hepatotoxicity of a test or unknown compound. (page 15, lines 17-19). In other words, each gene in the Tables 3A-3S is differentially expressed in liver cells or liver tissues after exposure to at least one hepatotoxin. It is thus clear that the genes in Tables 3A-3S are by no means randomly selected from various organs such as liver, heart, kidneys, testes, and brain as asserted by the Examiner. Rather, these are genes differentially expressed in liver tissues or liver cell samples when exposed to a toxic compound. The gene expression data of Tables 3A-3S are thus specific to liver toxicity as opposed to the toxicity of other organ tissues.

Further, Applicants would like to point out that controlling precedent requires that the US PTO must accept the objective truth of Applicants' teachings unless there is sound reason to doubt these teachings (MPEP § 2164.04). Applicants respectfully submit that there is no reason to doubt the objective truth of the statements contained within the Specification upon which Applicants rely for enabling support.

As a matter of Patent Office practice, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing the defining the subject matter sought to be patented must be taken as in compliance with the enablement requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein. In Re Marzocchi, 439 F.2d 220, 222 (CCPA 1971).

Under Marzocchi reasoning, the Specification must be taken as in compliance with the enablement requirement of 35 U.S.C. § 112 unless there is reason to doubt the objective truth of the Applicants' statements that each gene in the Tables 3A-3S is differentially expressed in liver cells or liver tissues after exposure to at least one liver toxin. The burden is on the Examiner to come forward with evidence as to why one of skill in the art would doubt this. Instead, the Examiner has merely made conclusory statements without any supporting evidence why Applicant's teachings for enablement should not be accepted as true. Without reliable evidence that refute Applicant's teachings, the rejection of the specification/claims under 35 USC §112, first paragraph for lack of enablement is contrary to well established law.

With regard to 3), Applicants respectfully submit that, contrary to the Examiner's assertion, the genes in Table 1 are all involved in liver toxicity. The Examiner's attention is directed to the arguments above under 1) and to page 40, lines 4-5, of the specification, where it specifically discloses that the genes in Table 1 are those "differentially expressed upon exposure to the named toxins."

With regard to 4), Applicants respectfully submit that claims 105 and 124 are dependent from claims 92 and 111, respectively. Both claims 92 and 111 recite a method of predicting for hepatoxicity of a test compound by preparing a gene expression profile from a liver tissue or liver cell sample exposed to the test compound. One of skill in the art would recognize that the liver tissues or liver cells set forth in steps (a) and (b) of claims 92 and 111 are normal liver tissues before they are exposed to the test compound or known hepatotoxin.

For these reasons, Applicants respectfully request that the pending rejection be withdrawn.

**Claim Rejections-35 U.S.C. § 112, First Paragraph (Lack of Written Description)**

Claims 92-129 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time of the invention was filed, had possession of the claimed invention. The Examiner asserts that the sequences disclosed in Tables 3A-3S are not all gene sequences and some of the sequences actually correspond to mRNA, cDNA, EST, and partial CDS sequences.

Without acquiescing to the Examiner's assertion, claims 92 and 111 have been amended to recite both gene sequences and ESTs. Support for the amendments can be found, for example, at page 43, line 1 or line 16 of the specification. In view of the amendment, Applicants respectfully request the rejection be withdrawn.

**Claim Rejections-35 U.S.C. § 102(b)**

The rejection of claims 92, 106 and 111 under 35 U.S.C. 102(b) as being anticipated by Farr *et al.* (US Patent 5,811,231) is maintained by the Examiner. In response to Applicants' arguments, the Examiner asserts that the amended claims do not explicitly recite "a single toxicity model" and therefore claims 92 and 111 only recite a random selection of ten genes from the sequences listed in Tables 3A-3S.

Applicants respectfully submit that there is no need to recite "a single toxicity model" in view of the term "any one of Tables 3A-3S." Applicants point out that the term "any one of Tables 3A-3S" does not have the same meaning as the term "any of Tables 3A-3S." While genes selected from "any of Tables 3A-3S" may be randomly selected from Tables 3A-3S, genes selected from "any one of Tables 3A-3S" must be selected from the same table, and thus are not randomly selected. More specifically, the ten genes recited in claims 92 and 111 must be selected from the same table, i.e., one of Tables 3A-3S. Because the ten genes from Farr *et al.* referred to by the Examiner do not correspond to the ten genes from any one of Tables 3A-3S as claimed, Farr *et al.* cannot anticipate any of the pending claims. The pending rejection under 35 U.S.C. § 102(b) should be withdrawn.

**Claim Rejections-35 U.S.C. § 103(a)**

Claims 92, 97-101, 111 and 116-120 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Farr *et al.* (US Patent 5,811,231). Further, claims 92, 97-101, 111, and 126 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over Farr *et al.* (US Patent 5,811,231) in view of Lashkari *et al.* (PNAS, 94:13057-13062).

The teachings and deficiencies of Farr *et al.* are discussed in the above 102(b) rejection and Applicants respectfully submit that this discussion is also pertinent to the rejections under 35 U.S.C. § 103(a). With regard to the first § 103 rejection, as discussed above, Farr *et al.*, do not disclose ten genes found in any one of Tables 3A-3S as claimed. As such, the claims of the present invention are not obvious in view of Farr *et al.*

With regard to the second § 103 rejection, the secondary reference, Lashkari *et al.* does not provide what Farr lacks. Lashkari *et al.* neither discuss preparation of a gene expression profile of at least ten genes as claimed nor discuss any method remotely related to Applicant's claimed method of predicting for the hepatoxicity of a compound using liver tissues or liver cell samples in any context. Accordingly, even if these references were properly combined (which Applicants do not concede), the combination of Farr and Lashkari does not provide Applicant's claimed methods. Applicants respectfully request the rejections be withdrawn.

**Conclusion**

Applicant respectfully requests reconsideration of the subject application in view of the amendments to the claims and the above remarks. It is respectfully submitted that this application is now in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this amendment, the Examiner is requested to contact the Applicant's undersigned representative.

If there are any fees due in connection with the filing of this amendment, please charge the fees to our Deposit Account No. 50-1283. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,
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Dated: 10/13/2006

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